DERMATOLOGICA SINICA 33 (2015) 234–238

Contents lists available at ScienceDirect

Dermatologica Sinica

journal homepage: http://www.derm-sinica.com

CASE REPORT

A rare presentation of adult T-cell leukemia/lymphoma with generalized cutaneous purpuric lesions

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ARTICLE INFO

Article history:
Received: Jan 5, 2015
Revised: Feb 1, 2015
Accepted: Feb 15, 2015

Keywords:
adult T-cell leukemia cells
adult T-cell leukemia/lymphoma
human T-cell lymphotropic virus type 1
purpura

ABSTRACT

Adult T-cell leukemia/lymphoma (ATLL) is an aggressive malignancy caused by human T-cell lymphotropic virus type 1. The disease is characterized by the presence of pleomorphic lymphocytes and cutaneous purpuric eruptions with skin, lymph node, visceral organs, central nervous system, and bone marrow involvement. We herein present the case of a 70-year-old man diagnosed with ATLL. The patient developed unique generalized cutaneous purpuric eruptions with systemic involvement including the gastrointestinal tract, peripheral blood, and bone marrow. Despite advanced chemotherapeutic treatment, he died about 5 months later due to a rapid progressive clinical course. Therefore, generalized cutaneous purpuric eruptions could be a poorer prognostic factor in the aggressive subtype of acute ATLL.

Introduction

Adult T-cell leukemia/lymphoma (ATLL) is an unusual form of post-thymic lymphoma associated with the retrovirus human T-cell lymphotropic virus type 1 (HTLV-1). A high rate of incidence of this disease is mainly reported in the Kyushu region of Japan. Other endemic areas are the Caribbean basin and Central Africa.[1] The onset age of ATLL in Japan is in the fifth decade of life, whereas in Brazil and Jamaica the onset age is in the fourth decade of life.[2] It has been suggested that ATLL occurs 20–30 years after the initial HTLV-1 infection in endemic areas.[1,2]

It is well-known that ATLL cells infiltrate into different systemic organs such as the gastrointestinal (GI) tract, liver, central nervous system (CNS), lymph nodes, peripheral blood, bone marrow, and skin.[3,4] Leukemic infiltration of different organs determines clinical presentations and morbidity.[5] The most common skin manifestations reported in different case series are patch, papules, plaque, or nodulotumoral lesions. Erythroderma or purpuric lesions could occur as rare cutaneous presentations in some cases.[6]

We herein report a rare case of ATLL presenting as generalized purpuric skin manifestations and discuss the clinical significance for the prognosis of ATLL.

Case report

A 70-year-old man with a medical history of chronic hepatitis B virus without any regular medication presented to our outpatient clinic with generalized purpuric skin eruptions for 1 week. The skin examination revealed generalized palpable purpura with confluence over the scalp, trunk, and four limbs (Figure 1A and B). These skin lesions were asymptomatic. He denied drug allergy or taking any new medication in the recent months. One month ago, he had epigastric pain and tarry stool. In addition, he also experienced other systemic symptoms (general weakness, weight loss, and arthralgia). Panendoscopy was performed, which revealed multiple gastric ulcers. Pathologic findings of the gastric ulcer revealed infiltration of atypical lymphocytes. Histopathologic examination of the purpuric skin over the back showed massive infiltration of pleomorphic atypical lymphocytes from the dermis to the epidermis (Figure 2A). There was extravasation of erythrocytes in the dermis and epidermis without apparent findings of vasculitis. Infiltration of neoplastic atypical lymphocytes was seen in the upper dermis with Pautrier microabscess (Figure 2B). Immunohistochemical studies of the abnormal lymphoid cells confirmed T-

Conflicts of interest: None.

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http://dx.doi.org/10.1016/j.dsi.2015.02.003

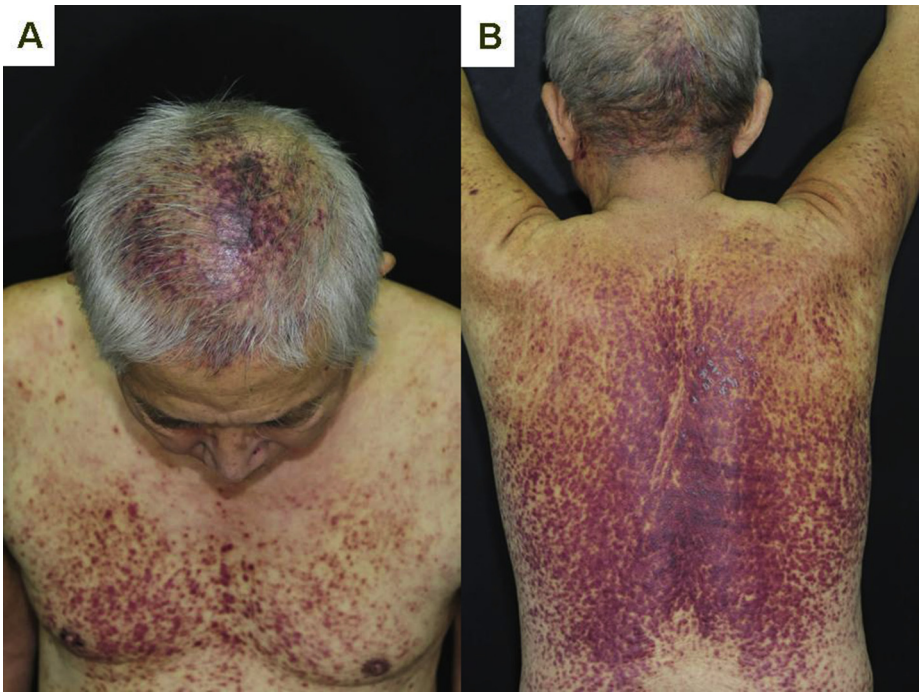

Figure 1 (A) Generalized asymptomatic palpable purpura with confluence over the scalp, anterior trunk, (B) posterior back, and four limbs.

cell lineages with positive results for CD3 and negative findings for CD20 and CD30 (Figure 2C and D).

Morphology of abnormal lymphoid cells in the peripheral blood smear showed abundant polylobulated “flower” cells (Figure 3A and B). The stomach biopsy specimen was examined, which revealed dense infiltration of the mucosa by atypical lymphocytes (Figure 4). The presence of HTLV-1 in patient's serum was confirmed by both enzyme-linked immunosorbent assay and Western blotting. Laboratory data revealed thrombocytopenia (platelet count, 73,000/μL), mild anemia (hemoglobin, 11.1 g/dL),

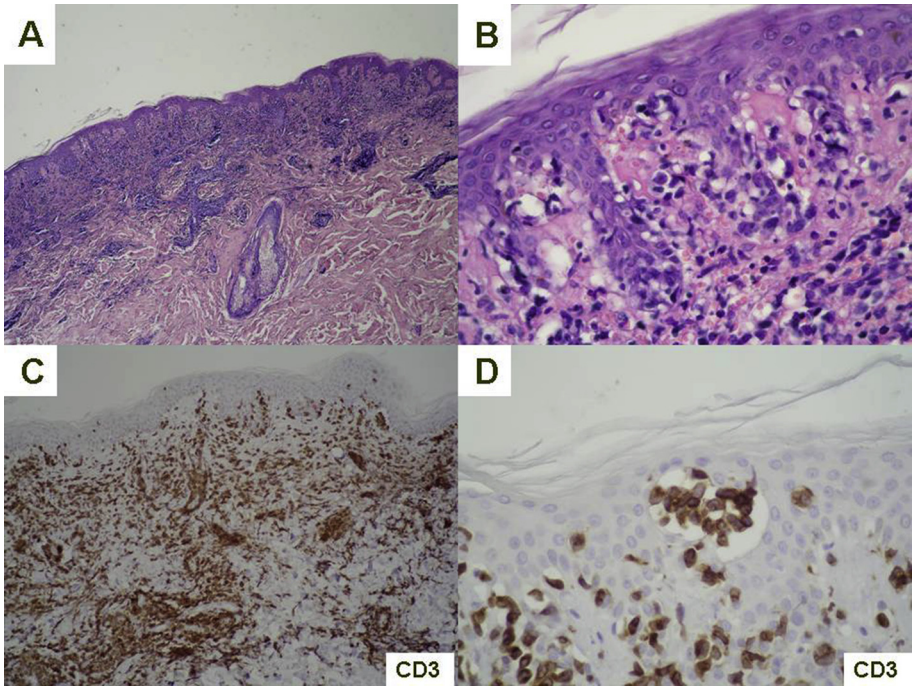

Figure 2 (A) Massive infiltration of pleomorphic atypical lymphocytes from the upper dermis to epidermis (hematoxylin and eosin, 40×). (B) High-power magnification shows extravasation of erythrocytes into the dermis and the epidermis, and epidermotropism of atypical lymphocytes with Pautrier microabscess (hematoxylin and eosin, 400×). (C) Immunohistochemical staining showed positive results for CD3 and negative findings for CD20 and CD30, which confirms the T-cell linage of lymphocytes (CD3, 100×). (D) Strongly positive CD3 atypical T lymphocytes with Pautrier microabscess (400×).

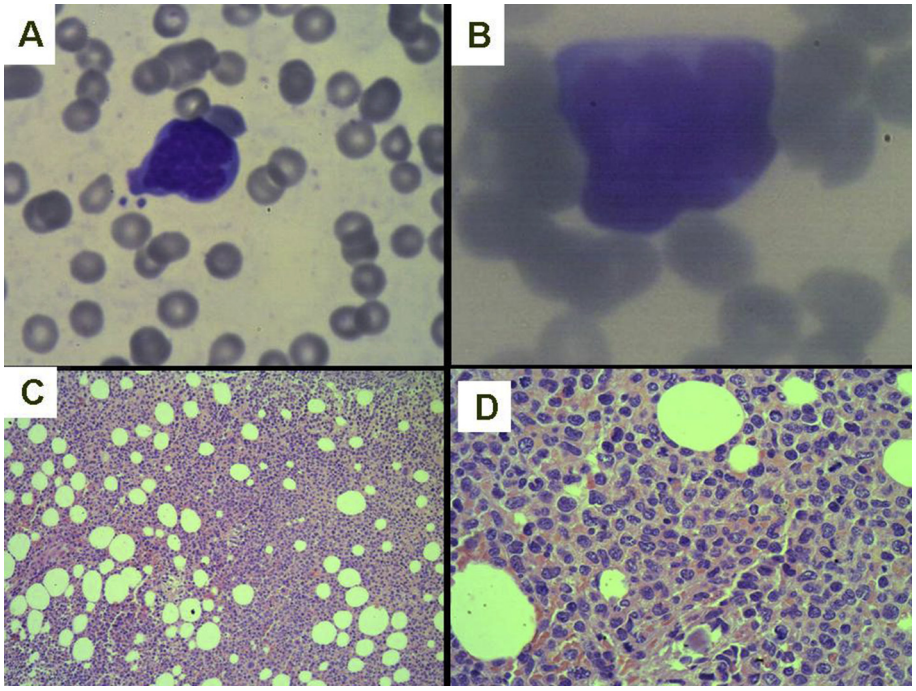

Figure 3 (A) Morphology of abnormal lymphoid cells in the peripheral blood smears showed abundant polylobulated "flower" cells (Wright stain, 400×). (B) High-power view of abnormal lymphoid cells (Wright stain, 1000×). (C) Pathology of bone marrow biopsy revealed diffuse atypical lymphoid cells in the bone marrow space (hematoxylin and eosin, 40×). (D) Atypical pleomorphic lymphoid cells in the bone marrow space (hematoxylin and eosin, 400×).

normal white blood cell count (6220/μL) with 7% atypical lymphocytes; however, the prothrombin time, activated partial thromboplastin time, and cryoglobulin were within normal limits. In addition, laboratory findings revealed other abnormalities including elevation of liver enzymes, alanine transaminase/aspartate transaminase (198/220 IU/L; normal range < 40 IU/L), marked elevations of *lactate dehydrogenase* (LDH; 1708 IU/L; normal range, 91–180 IU/L) and C-reactive protein (CRP; 9.7 mg/dL; normal range < 0.8), hypoalbuminemia (3.2 g/dL; normal range, 3.8–5.3 g/dL), and hypercalcemia (10.8 mg/dL; normal range, 8.4–10.2 mg/dL).

Radiologic imaging, bone marrow imaging, and cerebrospinal fluid aspiration were arranged for staging. Fluorodeoxyglucose-positron emission tomography imaging showed massive lymph

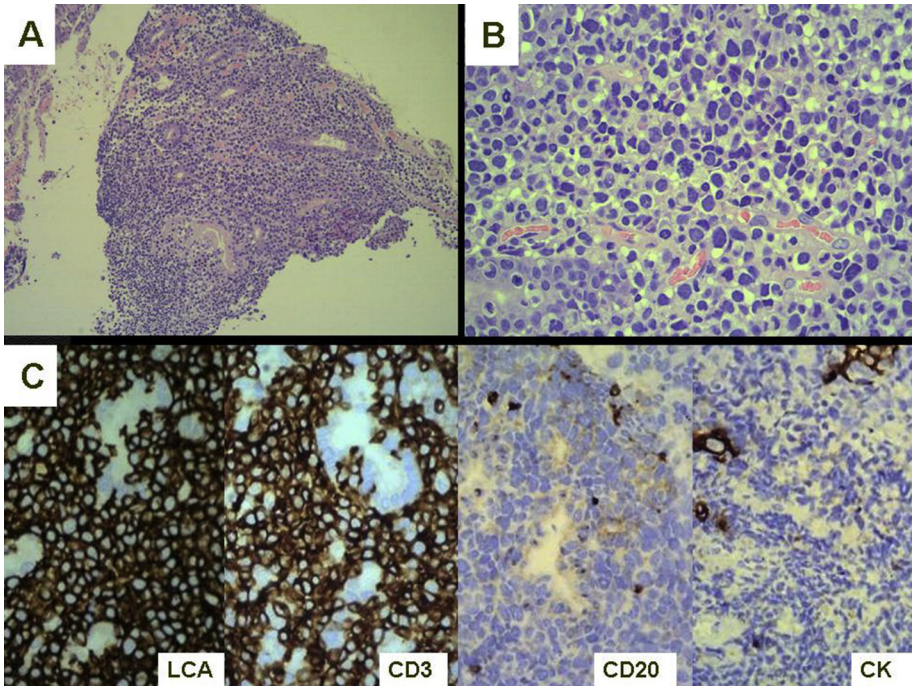

Figure 4 (A) Examination of the stomach biopsy specimen revealed dense infiltration of the mucosa (hematoxylin and eosin, 10×). (B) Atypical pleomorphic lymphocytes (hematoxylin and eosin, 400×). (C) Atypical lymphocytes are strongly positive for leukocyte common antigen (LCA) and CD3 but negative for CD20, CD34, cytokeratin (CK), and terminal deoxynucleotidyl transferase.

nodes in the left supraclavicular, bilateral para-aortic, and bilateral inguinal regions, and in the right shoulder joint, as well as increased fluorodeoxyglucose uptake over the bilateral lobes of the liver and the CNS. Bone marrow smear showed atypical proliferation of lymphoid cells and positive staining for CD45, CD1, and CD3, and negative staining for CD20, CD30, and cytokeratin (Figure 3C and D). Flow cytometric analysis of bone marrow aspiration for blasts showed 3.7% mature T lymphocytes, 3.5% B lymphocytes, and 2.7% natural killer cells with normal antigenic expression. Flow cytometric analysis of peripheral blood revealed 10.9% identical aberrant intermediate- to large-sized T cells, which were positive for CD2, CD3, CD4, CD7, and CD8, and negative for CD5 and CD56. Cerebrospinal fluid, cytologic findings, and cell block studies also revealed T-cell lymphoma with CNS involvement.

Based on the clinical manifestations and laboratory, imaging, and histopathological, and immunohistochemical studies, we diagnosed an aggressive subtype of acute ATLL (leukemic form) by the Shimoyama classification. We staged the tumor according to the Ann Arbor Staging Classification as T-cell lymphoma/leukemia stage IV with cutaneous, stomach, bone marrow, and CNS involvement. The patient was treated with serial chemotherapy regimens (cisplatin, etoposide, cytarabine, cyclophosphamide, vincristine, doxorubicin, gemcitabine, and methotrexate). He continued to receive these chemotherapy regimens for 4 months, but the response was poor. His condition deteriorated and he died 5 months after the initial presentation.

Discussion

ATLL is a rare and aggressive T-cell lymphoma associated with HTLV-1. HTLV-1 is also known to cause some vasculitides (uveitis and retinal vasculitis) and some chronic progressive diseases such as HTLV-1-associated myelopathy and HTLV-1-associated bronchopneumopathy.[3] These viruses could be transmitted by breast feeding, blood transfusion, sharing of needles, or sexual intercourse.[7] Approximately 2–5% of patients infected with the virus will develop ATLL. The incubation time from the HTLV-1 infection to the onset of ATLL has been estimated to be at least 20 years or more. It occurs in adults in the 20–80-year age group (average age, 58 years). The male-to-female ratio is 1.5:1.[8] The diagnosis of ATLL is based on HTLV-1 seropositivity and histologically and/or cytologically proven peripheral T-cell malignancy, as described in the World Health Organization classification.[9] Although the mechanism of malignant transformation is still unclear, the p40tax viral protein leads to transcriptional activation of many genes in HTLV-1-infected lymphocytes. In addition, the HTLV-1 basic leucine zipper factor plays an important role in T-cell proliferation and oncogenesis.[10,11]

According to the Shimoyama classification, there are four clinical subtypes of ATLL, including smoldering, chronic, lymphoma, and acute. The smoldering type has the best prognosis, followed by the chronic, lymphomatous, and acute types. The median survival times of the acute, lymphoma, and chronic types were reported to be 6.2 months, 10.2 months, and 24.3 months, respectively.[12] Death is caused by infectious complications. Our patient with elevated CRP level raised the possibility of concomitant infection, which also heralded a poor prognosis in this patient. The acute type of ATLL is characterized by massive lymph nodes, hepatosplenomegaly, lytic bone lesions, and multiple visceral lesions with skin, GI tract, and lung infiltration. Other important findings associated with the acute type of ATLL are hypercalcemia, elevated LDH levels, leukocytosis, and eosinophilia. Clinical subtypes, age, performance status, and serum calcium and LDH levels are the major prognostic factors for ATLL.

In fact, the skin is the most common extralymphatic site of involvement in 50% (43–72%) patients with ATLL.[6] The skin-infiltrating abnormal lymphoid cells are useful to investigate tumor cell biology in order to diagnose ATLL and predict a patient's prognosis. Primary cutaneous ATLL without systemic involvement has better clinical behavior and prognosis compared with secondary cutaneous ATLL. The majority of skin lesions are due to direct invasion of ATLL tumor cells, which may cause various types of eruptions.[12] The most common cutaneous lesions in ATLL patients are maculopapular eruptions or nodulotumoral lesions.[5,6] The rare cutaneous presentations could be erythroderma or purpuric lesions. The erythrodermic type had the poorest prognosis among all skin eruptions. Most patients with erythrodermic eruptions belonged to the acute type.

A secondary cutaneous ATLL with generalized purpuric lesions is an uncommon skin manifestation. The prognosis for the purpuric-type skin lesion is still unknown owing to its rarity. The production of granzyme B by ATLL cells may lead to the destruction of vessels and the development of purpuric eruptions in these patients.[13] Purpura could be the result of thrombocytopenia or dysfunction of platelets due to ATLL with bone marrow involvement without abnormal lymphocytes infiltration in the skin. Histologically, small vessels in the upper dermis are infiltrated by tumor cells (ATL cells), which may have caused tumor thrombosis without findings of vasculitis. Therefore, the mechanism of purpura formation in ATL is a matter of conjecture. To the best of our knowledge, only 11 cases of diffuse purpuric lesions resulting from ATLL cell infiltration have been reported to date. Ten of these cases occurred in Japan, and one case occurred in Brazil.[6] ATLL with specific purpuric lesions wound be more predominant in the acute clinical subtype (Table 1). According to Table 1, four of the 11 patients with localized purpuric changes had the smoldering subtype. Six of the 11 patients with generalized purpuric changes were in the acute stage. Therefore, generalized cutaneous eruptions with purpura could be a poorer prognostic factor in the aggressive subtype of acute ATLL.

Although Japan is one of the most important foci of HTLV-1 infection, it is not clear why neighboring regions such as East China or Korea have a low prevalence.[14] In Taiwan, slightly more data are available and the prevalence of HTLV-1 infection seems higher. HTLV-1 screening revealed the seropositivity rate of 0.058%. Furthermore, in the Taiwanese adult population aged > 30 years, the HTLV-1 prevalence varies from 0.82% to 1.63%.[15] ATLL in Taiwan is a rare malignant T-cell lymphoma with a very poor prognosis.[16,18] It is important for the dermatologists and physicians to be aware of ATLL in day-to-day practice. In summary, we reported a patient with primary gastric ATLL and secondary cutaneous ATLL. Acute-type ATLL with unusual generalized cutaneous purpura associated

Table 1 Previous reports of adult T-cell lymphoma/leukemia with specific purpuric lesions.

Study	Sex	Age	ATLL form
Present case	M	70	Acute
Oliveira et al 2011[17]	M	87	Acute
Okada et al 2007[4]	F	62	Acute
Tabata et al 2007[3]	M	76	Smoldering
Shimauchi et al 2005[13]	F	78	Acute
Slumauclu et al 2004*	M	78	Unknown
Adachi et al 2003*	M	62	Acute
Adachi et al 2003*	M	74	Smoldering
Masada et al 1999*	F	53	Smoldering
Katalura et al 1992*	M	34	Acute
Fukatani et al 1989*	M	55	Smoldering

ATLL = adult T-cell leukemia/lymphoma.
* References from Okada et al 2007.[4]

with GI, CNS, and lymph node involvement had a poor prognosis despite aggressive chemotherapy. Hypercalcemia and elevated LDH and CRP levels could have also been poor prognostic factors in our case. Diffuse purpuric lesions could be the first skin manifestation of ATLL, and increased attention is needed in this regard.

Funding/support

No funding was received for this study.

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